

REFERENCE

1. Tainter, M. L., Cutting, W. C., Wood, D. A., and Proeschner, F.: *Arch. Path.*, 18:881, 1934.

DISCUSSION

C. D. LEAKE, Ph. D. (University of California Medical School, San Francisco).—In extending Heyman's pharmacologic studies on the fever-producing properties of nitrated naphthols to include alphanitrophenol, Doctor Tainter and his associates recognized its probable extensive clinical application, particularly in obesity. They have been properly careful in repeatedly warning against its possible toxic reactions, and have carefully attempted to indicate what these may be by appropriate experimental studies. Unfortunately, the results of laboratory experimental work frequently do not coincide with what is often well-founded clinical opinion. Thus, it was pointed out by Anderson, Reed and Emerson (*Journal of the American Medical Association*, 101:1053, 1933), that Perkins had shown that munition workers exposed to dinitrophenol were particularly likely to show toxic effects if they had renal or hepatic disease or chronic rheumatism (*Public Health Reports*, 34:2335, 1919). French pathologists, according to Perkins, found fatty infiltration of the liver on postmortem examination on human beings presumably dying from dinitrophenol poisoning. Koelsch on experimental evidence thought dinitrophenol might cause fatty degeneration of the liver (*Zentralbl. f. Gewerbehyg.*, 4:261, 1927). Doctor Tainter and his associates now find in very careful experiments that the continued administration of dinitrophenol to dogs produces no significant liver injury. The situation reminds one somewhat of the discrepancy between clinical opinion and experimental evidence in regard to the effect of cinchophen on the liver, and also in regard to the problem of "alcoholic cirrhosis."

Certainly I think it is desirable to have all the evidence possible regarding opinions on the action of dinitrophenol. The fact remains, however, with respect to its clinical application, that it should be used with due respect for the fundamental clinical proposition that the hazard of treatment should never be permitted to exceed the hazard of the disease. Obesity is not a hazardous disease in any sense except in isolated instances. It would seem that the opinion of Anderson, Reed, and Emerson is still sound, namely, that "it is yet to be demonstrated that this drug is as safe and satisfactory for weight reduction in human beings as other methods in common use."

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H. CLARE SHEPARDSON, M. D. (384 Post Street, San Francisco).—The results obtained by the authors in attempting to ascertain what effect dinitrophenol has on the liver of the dog present no basis for criticism and little for discussion. It seems imperative that all knowledge possible be obtained concerning any substance which is to be used therapeutically in human beings. Yet a word of caution should be interpolated. It is questionable whether the physiology of the dog is identical with that of the human subject. Furthermore, it has been adequately demonstrated that the response of every human individual to dinitrophenol is not the same. Consequently, it must be remembered that not always can results obtained with animals be interpreted in such a manner as to offer complete assurance that the physiology of the human will be identically affected. The discussor has seen the icteric index (as determined clinically) considerably elevated by dinitrophenol. Whether this represents actual disturbance of liver function, or the presence of a yellow dye within the body, seems unimportant from a clinical point of view. What is important is the fact that the drug does this only to certain individuals who apparently are sensitive to it.

The authors are to be congratulated on furthering the investigation of the possible toxic effects of dinitrophenol, for it seems likely that it may eventually prove to have a place in the therapeutic armamentarium of the clinician.

W. W. BOARDMAN, M.D. (490 Post Street, San Francisco).—This study of the influence of dinitrophenol on the functional efficiency of the hepatic cells in dogs is of interest, but is contrary to the conclusion reached by MacBryde and Taussig after carefully controlled clinical studies. They find a definite decrease in the rate of excretion of phenolsulphonephthalein after moderate doses of dinitrophenol, which they interpret as indicating a toxic effect of the drug on the liver cells.

On the other hand, in the great number of patients who have taken dinitrophenol, there has been no satisfactory clinical evidence of liver damage, and further studies and the passage of time would be necessary to settle this question definitely.

However, dinitrophenol cannot be considered a therapeutic agent until its relationship to cataract formation has been satisfactorily explained. At present, around the San Francisco Bay region there are more than thirty known cases of cataract in relatively young women who have taken the drug, and cases are being reported from various points throughout the country.

The control of obesity, however extreme, does not justify this risk of cataract development.

CYANID POISONING: ADDITIONAL NOTE ON ITS TREATMENT WITH INTRAVENOUS METHYLENE BLUE SOLUTIONS*

By J. C. GEIGER, M.D.

AND

J. P. GRAY, M.D.

San Francisco

DISCUSSION by C. D. Leake, Ph. D., San Francisco; P. J. Hanzlik, M. D., San Francisco.

THE following case reports are presented as additional evidence of the efficacy of intravenous methylene blue solutions in the treatment of individuals affected by cyanid poisoning in which the drug has been ingested, and to describe an instance in which there was an unsuccessful attempt made to combat the effects of hydrocyanic acid gas poisoning.

REPORT OF CASES

CASE 1.—Mrs. D., age 28 years, was brought by ambulance into the Mission Emergency Hospital at 11:30 p. m., July 24, 1935. She was unconscious, and presented the following important signs: lowered body temperature ("cold" to touch), intense cyanosis, absence of a perceptible pulse (radial arteries), severe disturbance of respiratory function (four gasping respirations per minute) and "staring" eyes with dilated pupils. The patient's husband, who came with her to the hospital, stated that at about eleven o'clock she dissolved a lump of hard grayish-white substance (with a pungent odor) in some whisky in a glass tumbler, then drank the mixture. She then admitted to her husband that she had taken cyanid, soon after collapsed and became unconscious.

Artificial respiration and treatment for shock (warm blankets, elevation of the foot of the bed, and hot-water bottles) were administered, without apparent change in the patient's general condition, while the methylene blue solution was being prepared for intravenous injection. The administration of methylene blue (50 cubic centimeters of a one per cent solution) was begun at 11:45 o'clock. Within eight minutes after the methylene blue treatment had been initiated,

* Acknowledgment is made to reports of the various investigations made into the circumstances surrounding these events made by Milburn H. Querna, M. D., Avery E. Wood, M. D., San Francisco Hospital and Emergency Hospital staffs; William A. Sumner, M. D., Emergency Hospital staff; and A. B. Crowley, Chief Inspector, Division of Industrial Hygiene, all of the Department of Public Health.

the respiratory function had been restored sufficiently to permit the discontinuance of artificial respiration. Carbogen (oxygen 95 per cent, carbon dioxide 5 per cent) by inhalation was begun at this time, when respiration was slow, deep and labored, but spontaneous. At 11:50 o'clock, gastric lavage (using one per cent sodium thiosulphate solution) was initiated, and at 11:55 o'clock methylene blue (50 cubic centimeters of one per cent solution) was repeated. During the thirty-minute period immediately following, there was definite improvement of the respiratory and circulatory functions; pupils returned to normal size with normal reactions, and there was recovery of consciousness.

At 12:45 o'clock she was completely rational, and admitted having taken cyanid. (This was her fifth attempt at suicide, by various routes.) At one o'clock she was removed from the treatment room into the ward room, her condition being "practically normal, except for signs of nervous excitability." She slept well throughout the rest of the night, and at 7:30 o'clock (less than eight hours following treatment for cyanid poisoning) she wanted and felt that she was able to get up and to return to her work. Her condition continued to improve, and she was discharged from the hospital at 11:30 a. m., twelve hours after entry.

Chemical study of the gastric contents showed the presence of cyanid, and examination of a portion of the remaining original "grayish-white substance (with a pungent odor)" showed that it was sodium cyanid. Blood samples were not obtained and quantitative studies were not carried out.

In the instance reported, the successful use of methylene blue solutions, intravenously, in the treatment of an individual affected by cyanid poisoning occurring as a result of the ingestion of cyanid, is well demonstrated. It is believed appropriate to record, also, at this time, an unsuccessful attempt at the treatment of an individual affected by hydrocyanic acid-gas poisoning.

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CASE 2.—Mr. W., age 45 years, was brought into the Harbor Emergency Hospital at 10:55 o'clock on the morning of November 21, 1934. On arrival the outstanding signs of poisoning were extreme cyanosis, unconsciousness, rapid thready pulse (radial arteries), and markedly disturbed respiration (weak gasping breathing at the rate of one to two per minute). There was a strong odor of cyanid about the patient.

As soon as it could be prepared, methylene blue (50 cubic centimeters per one per cent solution) was given intravenously, epinephrin (one cubic centimeter of a 1:1000 dilution) and caffein-sodio benzoate (one gram) subcutaneously. With the completion of the administration of methylene blue, epinephrin (one cubic centimeter, 1:1000) was repeated, this time by the intracardial route, and artificial respiration was begun (with the patient in the prone position).

Within a period of approximately three minutes after the initiation of artificial respiration, there was a resumption of spontaneous respiration of deep and regular character at the rate of about 18 to 20 per minute. The pulse rate approximated 90 per minute and was of good quality, and cyanosis was much less intense.

At 11:10 o'clock his condition was quite good; and, after being wrapped in warm blankets, the patient was taken from the treatment room and was placed in bed. Ten minutes later, at 11:20 o'clock, there occurred an increase in the pulse rate, a greater intensity of the cyanosis, and labored respiration. These changes were believed sufficient to warrant further use of methylene blue, and 40 cubic centimeters of the one per cent solution was given intravenously, with subsequent improvement of the quality and rate of the pulse, and noticeable improvement of the respiration function.

Shortly afterward, however, the patient began to struggle, trying to get out of bed, with such force that two persons were required to hold him. At 11:40 o'clock carbogen inhalation was instituted. At 11:45

o'clock his physical activity was so violent that restraint became necessary. At this time he responded, slightly, to his brother's questioning. Because of the fact that his strength was being rapidly exhausted by his struggling against restraint, morphin sulphate, 16 milligrams (grains one-quarter) was given at 11:50 o'clock. At 12 o'clock noon, there was a sudden change, with cessation of respiration and very feeble pulse. Artificial respiration, in conjunction with carbon dioxide and oxygen, was reinstituted and continued for more than an hour without success. During this last hour the character of the pulse temporarily improved at times, and an occasional spontaneous respiratory movement occurred; but in the intervals between these hopeful signs the patient's entire body would undergo tetanic convulsions, resulting in cessation of respiratory movement and marked weakening of the heart action, as evidenced in the character of the pulse. Death occurred at 1:10 o'clock, before sodium amytal, which was being prepared for injection, could be administered, or two and one-quarter hours after the patient was brought to the hospital.

Autopsy was conducted by the necropsy surgeon to the coroner, and examinations of the blood and tissues were carried out by the toxicologist and the pathologist of the coroner's office, with positive findings limited to the odor of cyanid from the markedly congested liver, and evidence of injections of methylene blue in the antecubital fossae.

COMMENT

Chemical examination of the blood failed to show the presence of cyanid, but this result should be more or less expected, since cyanhemoglobin, which is formed very rapidly in the presence of cyanid in the blood, is not demonstrable in blood from the living subject by methods now available. It is doubtful, also, whether spectroscopic studies for methemoglobin, or even the chemical examination of the urine for sulphocyanates, would be fruitful in so short a period of time after the poisoning occurred.

Mr. W. was a fumigator, and at the time of the incident which resulted in his death was at work fumigating, with hydrocyanic acid gas, the engineers' quarters on an intercoastal liner, docked at her pier in San Francisco. The gas was generated, on the pier, by the addition of a commercial product ("cyan-egg") to dilute sulphuric acid, the resultant gas being pumped through a hose to the quarters being fumigated. Mr. W., presumably, stooped over a hose-coupling to repair a leak and breathed in sufficient quantities of hydrocyanic acid gas, within a very short period of time, to cause his death; but since the leaking coupling referred to was on the open deck, in the open air, it is controversial, we believe, whether these conditions would permit hydrocyanic acid gas to be absorbed in sufficient quantities to result in severe poisoning and death. Investigation showed, also, that the first sign of distress was in evidence when Mr. W., while working over the leaking coupling, after having sealed up the quarters being fumigated and signaled for the "shooting" of the gas, reached in his overalls pocket and withdrew an ammonia capsule, stating to his brother, "I think I had better use this." He was unable to crush the capsule, however, collapsing immediately after making this statement to his brother. It is also of interest to note that, as far as could be determined at the time, no gas mask was in evidence in the close proximity of the quarters being fumigated.

These points are mentioned because of the very real hazard that exists, and the possibility that Mr. W., discovering leaks in the quarters fumigated, might have been exposed to concentrations and time intervals beyond safety limits during the period of repairing these leaks, after the release of the gas in the closed space.

ON USE OF HYDROCYANIC ACID GAS AS A FUMIGANT

The use of hydrocyanic acid gas as a fumigant is quite widely practiced, and although it meets the requirements of an effective agent, it carries, at the same time, a very low factor of safety. Competent regulation and supervision of all crews using this method of fumigation is essential at all times if deaths are to be prevented. An effective ordinance has been operative in San Francisco for more than three years; and under this legal instrument, rigorous supervision obtains in all fumigations in which a dangerous poisonous gas is used. A trained inspector is present before and during the "shooting" of the gas, and final release of the premises occurs only with his approval. Every precaution is taken, including proper sealing material and adequate sealing, complete inspection for persons and animals on the premises fumigated and adjacent premises as well, of appropriate gas masks and other necessary safety and working equipment. During the years that the current ordinance has been in effect, no deaths due to hydrocyanic acid gas, as used in fumigation, have occurred within the city and county of San Francisco, which comprises the area under the supervision of the Department of Public Health, although this gas has been so applied as a fumigant to a not inconsiderable extent. In the instance cited the work was done at a point outside the area under the jurisdiction of the Department and the ordinance, therefore, was not operative.

It cannot be too strongly emphasized that there is a genuine hazard, potential and real, in every job in which hydrocyanic acid gas is used as the fumigant.

IN CONCLUSION

It is apparent, from our experience in this one instance at least, that, while methylene blue solutions are of undoubted and even life-saving value in the treatment of those affected by cyanid poisoning due to the ingestion of cyanid, it probably offers very much less as an antidote against hydrocyanic acid gas.

Department of Public Health,
101 Grove Street.

DISCUSSION

C. D. LEAKE, Ph. D. (University of California Medical School, San Francisco).—The report of Doctors Geiger and Gray on a fatal case of poisoning by hydrocyanic acid gas is very timely. The gas is widely used in fumigating, and in spite of many precautions it constitutes a severe, industrial hazard. The action of cyanid, like that of other acute poisons, is dependent on the rapidity with which a toxic concentration is reached in the cells of the body upon which it acts. The classic work of Lovenhart (summarized particularly in *Archives of Internal Medicine*, 21:109, 1918) showed that the tissues most susceptible to cyanid are those of the medullary centers. Cyanid is much more rapidly absorbed when inhaled as a gas than when in-

gested as the sodium salt through the stomach. A great mass of experimental evidence has accumulated to show that methylene blue protects in cyanid poisoning by forming methemoglobin, which then combines with cyanid to form cyanhemoglobin (Hug and Chen, *Amer. J. Med. Sci.*, 188:767, 1934; Haggard and Greenberg, *J. A. M. A.*, 100:2001, 1933; Hanzlik and Richardson, *J. A. M. A.*, 102:1740, 1934; and Wendel, *Jour. Pharm. Exper. Therap.*, 54:283, 1935). The fact still remains, however, that this work does not rule out the possibility that methylene blue may act by replacing cellular respiratory catalysts, which are known to be inactivated by cyanid, as proposed by Brooks (*Proc. Soc. Exper. Biol. Med.*, 29:1228, 1932), and applied clinically by Geiger (*J. A. M. A.*, 101:269, 1933). An important factor, neglected by the experimental proponents of the methemoglobin formation theory, is that methylene blue will not form methemoglobin until hemolysis of red cells occurs. This observation was made in our laboratory two years ago, but was never reported. Hemolysis with methylene blue requires from half an hour to an hour to take place. The rapidity of clinical improvement on methylene blue administration in cyanid poisoning suggests that the dye does not act only by virtue of methemoglobin formation. On intravenous injection, methylene blue should not exceed a dosage of 25 mgm./kg. More than this may be toxic.

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P. J. HANZLIK, M. D. (Stanford University School of Medicine, San Francisco).—This additional note by Doctors Geiger and Gray continues a commendable practice of reporting results with a new plan of treating cases of poisoning which has created a nation-wide interest. It is to the everlasting credit of Doctor Geiger that he, an alert public health official, has taken advantage at every opportunity of the achievements in medical research for the best interests of the public. Otherwise, methylene blue in cyanid poisoning might still be only an interesting experimental demonstration. But today there is no longer any doubt that this dye has become a useful life-saving measure, thanks largely to our conscientious colleagues of the San Francisco Department of Public Health.

The results in the first case reported by Drs. Geiger and Gray confirm, of course, the value of methylene blue in cyanid poisoning, but the authors appear to be doubtful of its value in the second case, where hydrocyanic acid vapor was concerned. The chances of successful treatment of cases of poisoning from hydrocyanic vapor are undoubtedly much more limited than those from swallowing potassium or sodium cyanid. However, a lack of success in poisoning from the vapors is to be ascribed to a rapidly fatal action, the result of a highly efficient pulmonary absorption, and not to any inherent peculiarity or difficulty in the actions of methylene blue under these conditions. Fundamentally, the actions of the cyanogen (CN) group are the same whether inhaled, injected, or swallowed, and methylene blue also acts the same way on the blood under all these conditions. The time element in the treatment is the most important consideration. If an injection of methylene blue can be made promptly, and before the hydrocyanic acid has completed its poisonous action, the same beneficial result should follow as when it is injected after the taking of cyanid. According to the report, methylene blue was successfully given twice in the second case, and the immediate reactions both times were favorable, as might be expected. The patient was temporarily improved, but presently got worse. It is at this point where a legitimate difference of opinion might arise as to continuation of the same, or selection of another, treatment. It is possible that further relapses might have been stopped, if the treatment with methylene blue had been continued, or changed to injections of sodium nitrite and thiosulphate. The latter combination is more efficient as a methemoglobinizer than is methylene blue. On the other hand, it is entirely possible that the functional efficiency of the respiratory center was so low (and for that matter other functions as well) as the result of an apparently pro-

longed exposure to the hydrocyanic vapor, that no kind or amount of treatment could have restored the physiologic state. In other words, the various physiologic functions might have been irreversibly inhibited or poisoned by the cyanid. Under these conditions the use of sedatives would, in my opinion, be contraindicated. It is conceivable that the cause of death in this case was not the result of exposure to the hydrocyanic vapors, because the rule is a rapidly fatal action or a rather prompt recovery, but to some other cause.

As far as I know, most authorities deny the rapid formation of cyanhemoglobin from an action of the cyanogen (CN) directly on blood. Although a slow formation has been postulated, this is contrary to the generally accepted view that cyanhemoglobin forms only in the presence of methemoglobin. It is the rapid formation of the innocuous cyanmethemoglobin (cyanhemoglobin) which explains the benefit derived from the injection of methylene blue, which, first of all, converts oxyhemoglobin of the blood to methemoglobin.

It is true, as stated by Drs. Geiger and Gray, that a spectroscopic examination of the blood for methemoglobin would be of doubtful value, because this is not a sensitive method. But a determination of the oxygen capacity of the blood would show a reduction, a virtual proof of the presence of methemoglobin, as has been demonstrated in animals. I agree with the authors that chemical examination for cyanid in the blood and tissues is futile, even in rapidly fatal cases, owing to the swift oxidation of this ion to oxycyanate and sulfo-cyanate.

There is no doubt of the greater value of protective measures than of running a risk of poisoning and depending on antidotal measures for eliminating the hazards accompanying fumigation with hydrocyanic vapors. The procedures used under the supervision of the San Francisco Department of Public Health are to be commended for their success. The careful consideration of every detail in the conduct of fumigation operations, and the warnings given by this department, testify again to a keen appreciation of the scientific management of, and a deep concern about, all matters pertaining to the public welfare.

THE LAW OF INCOMPETENCY*

By R. LEE CHAMBERLAIN †
San Francisco

PERSONS of unsound mind have always received special protection under our law. This special protection is codified in California as Sections 38, 39 and 40 of the Civil Code, which provides that:

"A person entirely without understanding has no power to make a contract of any kind, but he is liable for the reasonable value of things furnished to him necessary for his support or the support of his family."¹

On the other hand, "a conveyance or other contract of a person of unsound mind, but not entirely without understanding, made before his incapacity has been judicially determined, is subject to rescission . . ."² and

"After his incapacity has been judicially determined, a person of unsound mind can make no conveyance or other contract, nor delegate any power or waive any right, until his restoration to capacity. . . ."³

CONNOTATION OF "NON COMPOS MENTIS"

The words "insane," "incompetent," "unsound mind," are all expressed in law by the term *non*

compos mentis; but this term has no exact meaning: it includes all kinds of mental unsoundness recognized by the law, and its meaning varies with the type of matter under consideration.

In a medical sense, insanity or unsoundness of mind may be anything short of a mind wholly normal and free from any defective coördination arising from any cause. With the law we are only concerned with that degree of variation from the normal as will put in operation the law's protection applicable to the particular case to be considered.⁴

There is the degree of unsoundness of mind, which has to deal with the responsibility of the individual for crime. When dealing with crime, the law is concerned with ascertaining whether the individual, at the time of the commission of the alleged crime, had sufficient mental capacity to distinguish right from wrong, as applied to the particular act in question. In a criminal trial, too, the law is concerned with the ability of the person charged to properly conduct his defense at the time of trial.

Again, in civil actions the law is concerned with different degrees of unsoundness of mind; for, as has been noted, if the person in question is entirely without understanding the contract is void, while if not entirely without understanding the contract is voidable. The principal difference between a void and a voidable contract is that in a voidable contract the consideration received must be returned or tendered.⁵

There are two principal forms of court proceedings with which you are all undoubtedly familiar, for in both expert testimony on mental competency plays an important part.

COURT PROCEDURE IN COMMITMENT TO A STATE HOSPITAL

There is the commitment to the state hospital, where the question to be determined by the court is whether the individual before the court is "so far disordered in his mind as to endanger health, person, or property . . ."⁶ for, if so disordered, he should be confined in a state hospital until recovery, when he will be discharged by the medical superintendent of the hospital.

COURT PROCEDURE IN APPOINTMENT OF A GUARDIAN

The other court proceeding is the appointment of a guardian where the question to be determined by the court is whether the alleged "incompetent person" is unable unassisted to properly manage or take care of himself or his property and, by reason of such incompetency, is likely to be deceived or imposed upon by artful or designing persons.⁷

This latter proceeding is important, because it is this judicial determination of incompetency that is referred to in Section 40, Civil Code, when it says: "After his incapacity has been judicially determined, a person of unsound mind can make no conveyance or other contract, nor delegate any power or waive any right, until his restoration to capacity."

* Read before the Neuropsychiatry Section of the California Medical Association at the sixty-fourth annual session, Yosemite National Park, May 13 to 16, 1935.

† Deputy Attorney-General, State of California.